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# Options to Distinguish Heroin and Poppy Seed Use



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19 ABSTRACT (Continue on reverse if necessary and identify by block number)

Three options are proposed to distinguish between opiate positives in the Navy drug deterrence program arising from Heroin and poppy seed use. These options consist of 1) detection of Thebaine, which is only present in poppy seeds; 2) detection of 5-acetylthebaol, which is only present in Heroin; and 3) detection of various cutting agent in Heroin. Discussions of the applicability and liability of each of these options are presented.

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# OPTIONS TO DISTINGUISH HEROIN AND POPPY SEED USE

## Background

Levels for opiate positives in the Navy drug deterrence program were raised from 300 ng/ml to 4000 ng/ml for morphine and 2000 ng/ml for codeine in an attempt to distinguish between poppy seed use and Heroin abuse. When the morphine levels were between 300 ng/ml and 4000 ng/ml, the urine also was tested for the presence of 6-acetylmorphine (a Heroin metabolite). If 6-acetylmorphine is present then that urine sample would be considered positive for Heroin. After examining a number of samples between the levels of 300 ng/ml and 4000 ng/ml of morphine, no 6-acetylmorphine was found. Therefore, testing for 6-acetylmorphine when the morphine levels were low has been recently discontinued. Testing for 6-acetylmorphine when the morphine level is above 4000 ng/ml is still continuing.

During several inspections of the Navy Drug Screening Laboratories (NDSL), the issue that the Navy was possibly excluding Heroin positives since the rate of metabolism and excretion of 6-acetylmorphine was much faster then Heroin. The faster metabolism would imply that if the morphine level was lower than 4000 ng/ml, if would be likely that no 6-acetylmorphine would be detected and therefore the Heroin abuse would go undetected.

A study was requested at the March 17th meeting of the *Ad Hoc* urinalysis committee meeting by Captain Cangianelli (U.S. Navy; Director, Drug and Alcohol Abuse Prevention and Control Division) to address the detection of poppy seed use vs. Heroin abuse when morphine levels are below 4000 ng/ml by detecting markers other than 6-acetylmorphine. This report attempts to address those issues.

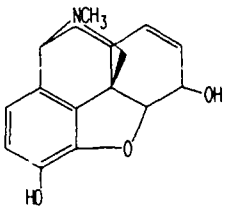
## Discussion

The structures of the major opium alkaloids are shown in Figure 1, as a reference. Considerable information exists about species present in Heroin and opium. The Drug Enforcement Administration has for a number of years been examining Heroin and opium seizures for the alkaloid content and patterns. From these patterns, the origin of the Heroin can be determined. Also, the different alkaloid patterns from various drug seizures can be compared to determine if they came from the same source. Part of that data is given in Table 1. The ratio of the minor alkaloids to the morphine is also presented which shows considerable variation, depending on the source of the opium. Only recently have standards been available to allow the quantitation of the components of the Heroin or opium. In earlier work, only qualitative comparisons were made.

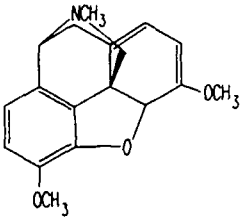
Less is known about the alkaloids found in poppy seeds. Data from two studies is shown in Table 2 along with the ratios of the minor alkaloids to morphine. The agreement between these two studies is poor. This may reflect the different extraction techniques used to extract the alkaloids rather than the natural variations in the alkaloid content. The extraction of the opiate alkaloids from poppy seeds is difficult due to the high content of poppy seed oil.

Manuscript approved May 8, 1989.

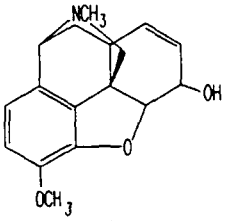
**Figure 1 - Opium Alkaloids**



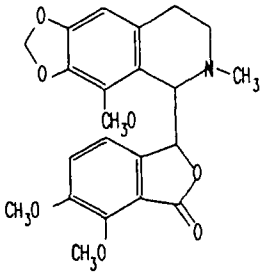

Morphine



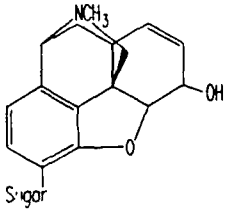

Thebaine



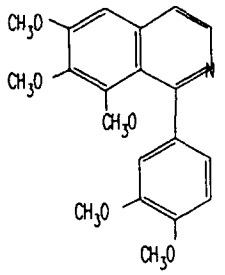

Codeine




Noscapine




Morphine Sugar Conjugate




Papaverine

**Table 1 - Alkaloids in Opium***

| Sample | Morphine | Codeine | %Ratio | Thebaine | %Ratio | Papaverine | %Ratio | Noscapine | %Ratio |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 15.0 | 4.15 | 28 | 1.95 | 13 | 2.22 | 15 | 9.44 | 63 |
| 2 | 11.7 | 1.75 | 15 | 4.74 | 41 | 1.4 | 12 | 4.84 | 41 |
| 3 | 10.4 | 4.89 | 47 | 6.73 | 65 | 3.15 | 30 | 6.74 | 65 |
| 4 | 16.1 | 2.53 | 16 | 3.74 | 23 | - | | 5.74 | 36 |
| 5 | 14.9 | 2.17 | 15 | 5.03 | 34 | - | | 5.55 | 37 |
| 6 | 13.8 | 4.10 | 30 | 1.65 | 12 | 2.18 | 16 | 10.6 | 77 |
| 7 | 15.3 | 2.58 | 17 | 2.86 | 17 | 0.52 | 3 | 7.32 | 48 |
| 8 | 15.1 | 2.21 | 15 | 2.91 | 19 | 0.50 | 3 | 7.27 | 48 |
| Range | | | 15-47 | | 12-65 | | 3-30 | | 36-77 |

*From: A.R. Sperling, J. Chrom., **294** 297(1984).

**Table 2 - Alkaloids in Poppy Seeds**

Study 1 (% of alkaloids)*

| Sample | Morphine | Codeine | %Ratio | Thebaine | %Ratio | Papaverine | %Ratio | Noscapine | %Ratio |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 0.503 | 0.117 | 23 | - | - | 0.095 | 19 | 0.133 | 3 |
| 2 | 0.559 | 0.107 | 19 | 0.061 | 11 | - | - | 0.186 | 33 |
| 3 | 0.699 | 0.051 | 15 | - | - | - | - | 0.019 | 3 |
| 4 | 0.812 | 0.099 | 12 | 0.043 | 5 | 0.301 | 37 | - | - |

Study 2, ($\mu$g/g poppy seeds)#

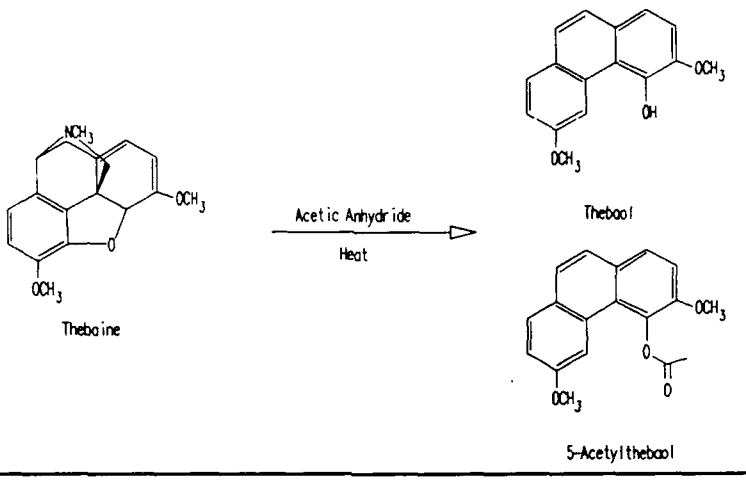
| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 5 | 19 | 0.8 | 4 | 1.5 | 8 | - | - | | |
| 6 | 106 | 3.8 | 4 | 14 | 13 | 3.6 | 3 | | |
| 7 | 5.1 | 0.1 | 2 | 0.3 | 6 | - | - | | |
| 8 | 24 | 0.36 | 2 | 0.46 | 2 | 0.045 | 0.2 | | |
| Range | | | 2-23 | | 2-11 | | 0-37 | | 3-33 |

*From: V. Tibor, Magyar Kemiai Folyoirat **92** 54(1986).
#From: H.N. El Sohly, D.F. Stanford, A.B. Jones, M.A. El Sohly, H. Snyder, and C. Pederson, J. For. Sci., **33** 347(1988).

**Thebaine as a Marker of Poppy Seed Use**

Heroin is derived from acetylation of the alkaloids found in opium, which are similar to those in poppy seeds. As such, the alkaloids found in Heroin should reflect the ones found in opium and poppy seeds. However, thebaine is not found in Heroin because it is decomposed primarily to 5-acetylthebaol during the acetylation process under the strongly acetic conditions normally employed (see Scheme 1). Thus the absence of thebaine should be a marker of Heroin use; and its presence should indicate poppy seed use. For practical analysis the thebaine/morphine ratio would be determined. If this ratio fell below the value (plus a safety margin) found in poppy seeds, than that urine specimen would be considered positive for Heroin.

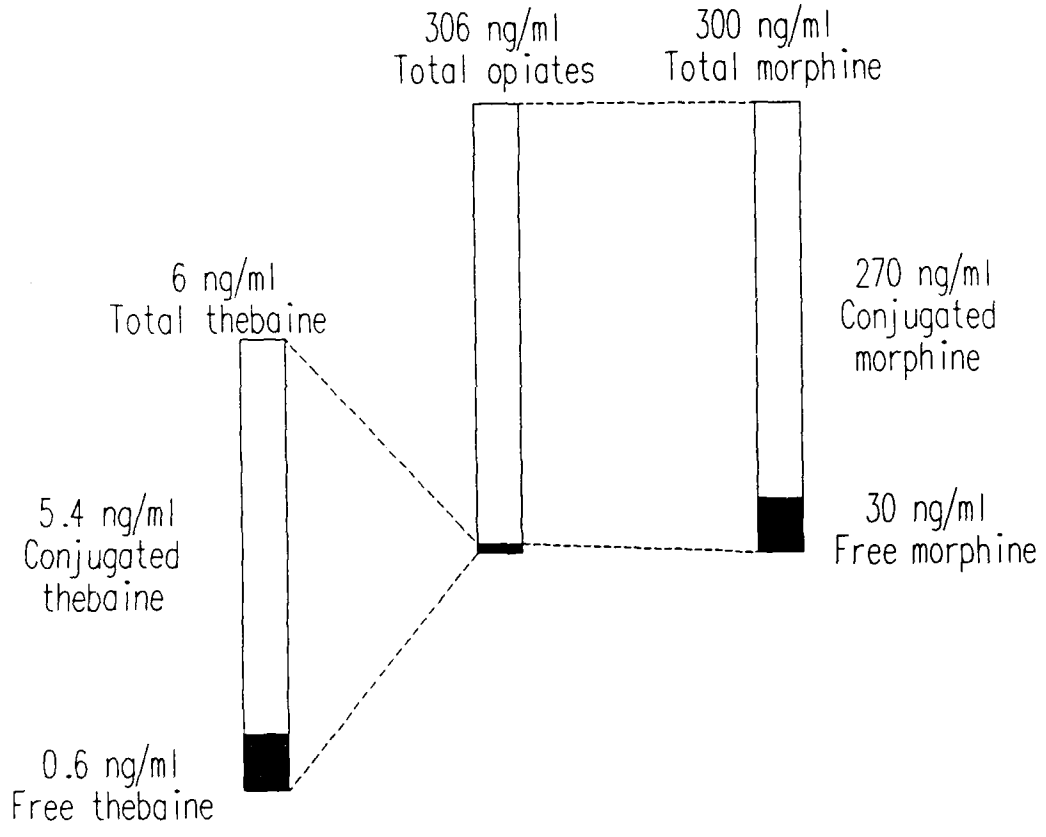
**Scheme 1 - Decomposition of Thebaine**




Three problems exist if thebaine is to be used as a marker. The major problem is that the PRESENCE of thebaine indicates poppy seed use and NOT Heroin use. Therefore, the presence of a compound (or more accurately the ratio of thebaine to morphine) would be the determination of Heroin use. Little is known of about the metabolism of thebaine. Based on its structure (see Figure 1), one would expect thebaine to be metabolized in a similar manner to the alkaloids codeine and morphine. Tests would need to be done to establish this fact. Likewise, the thebaine, morphine and codeine content in a large number of samples of poppy seeds would need to be measured to determine the ranges that occur.

The difficulty in measuring low levels of thebaine likely to occur in the users of poppy seeds can be appreciated by referring to Figure 2. This is a hypothetical case of a poppy seed user, the total opiate levels were 306 ng/ml. Of this amount, 300 ng/ml was be morphine so the sample would be considered positive using the old cut-off level. The total thebaine level would be 6 ng/ml (2% of the morphine and assuming a similar metabolism) and the free thebaine level would be only 0.6 ng/ml. These low levels are difficult to detect and therefore thebaine may be missed. The detection of thebaine would be <u>critical</u> for this hypothetical poppy seed eater since the presence of thebaine would prove his innocence.

**Figure 2 - Comparison of the Relative Concentrations of Morphine and Thebaine in a Hypothetical Poppy Seed User**



The second problem was indicated in a study done by El Sohly. He looked at thebaine as a marker of poppy seed ingestion and did not find FREE thebaine in the urine of poppy seed users. Morphine is excreted mostly as the glucuronide (where a sugar is attached by the body to make the morphine more water soluble, see Figure 1). Thebaine would also be expected to be excreted as the glucuronide as well, due to its structural similarity to codeine and morphine. In the analysis of morphine in urine, the glucuronide is cleaved by heating the urine with strong acid. This frees the morphine and allows its extraction with organic solvents. Without cleavage, little morphine would be detected. However, thebaine would be unstable to these acid conditions (that is why it is not present in Heroin because the acetylation, i.e. acid, destroys it). Enzymes could be substituted for the acid hydrolysis which would allow the determination of both morphine and thebaine. Acid hydrolysis was used in El Sohly's paper and thus conjugates of thebaine could not be determined.

The third problem may be with casual users of Heroin. They could use Heroin on Friday, eat poppy seeds on Sunday, be tested on Monday and look like a poppy seed user. In this case, the individual would have a relatively low level of morphine from the Heroin and high levels of thebaine and morphine from the poppy seeds. Thus the morphine/thebaine ratio might well fall within that expected from poppy seeds and therefore this individual would have defeated the deterrence program. However, there is a good chance that this individual would defeat the present program with the morphine cut-off levels at 4000 ng/ml. It is highly unlikely that this level would be present on Monday for a low-dose user on the past Friday.

**Thebaol and 5-Acetylthebaol as a Marker of Heroin Use**

The techniques used in the production of Heroin vary tremendously in different parts of the world. Generally, morphine is extracted from opium and partially purified. The extract is subjected to acetylation with acetic anhydride and pyridine with heating. This produces a dark reaction mixture, which is diluted with water, base is added to precipitate the Heroin, and the Heroin is collected. As mention above, thebaine is decomposed in this process. The 5-acetylthebaol and other byproducts float to the surface as a black scum when the water is added. This scum is sometimes removed and sold as a low grade Heroin in the countries of manufacture. This material is usually smoked. The heroin that is precipitated by the base is still highly colored and must be further purified by recrystallization. In the Middle East and Mexico, the Heroin is poorly purified of the degradation products formed in the acetylation process and therefore is colored. Mexican Heroin is the least purified and is black in color, hence the name 'Black Tar Heroin'. Heroin produced in the Middle East is partially purified and is tan in color. Heroin produced in Asia is highly pure and white in color. Asian Heroin tends to be recrystallized from ethyl alcohol and has no degradation products of thebaine. The other sources have varying amounts.

According to Donald Cooper of the Drug Enforcement Administration Special Testing and Research Laboratory, the concentrations of thebaine degradation products vary depending on the source of the Heroin. Their analyses of various Heroin samples shows from 1% to .01% 5-acetylthebaol in Heroin from Mexico and the Middle East whereas in Heroin from Asia, the 5-acetylthebaol is undetectable. Approximately 70% of the Heroin in the United States originates from the Middle East and Mexico. Thus we can expect 5-acetylthebaol or thebaol

would be detectable in at about 70% of the urine samples suspected of being positive for Heroin. This ratio would be highly dependent on what part of the US the sample originated as Asian Heroin tends to be distributed only in California and New York.

The metabolism of 5-acetylthebaol in humans is unknown. However, due to its structural similarity to codeine, one would expect 5-acetylthebaol to be deacylated by the body and the hydroxyl group to be conjugated to a sugar residue to make it water soluble and excretable. Whether or not the 5-acetylthebaol is even injected by Heroin users is unknown. It is much less water soluble than Heroin and may not be dissolved when the Heroin is prepared for injection. However, since addicts tend to inject all the hit, the insolubility of 5-acetylthebaol may not be a problem.

The ratio of 5-acetylthebaol to morphine is low and a similar argument given for thebaine would apply. If the Morphine level were at the old cut-off concentration of 300 ng/ml the 5-acetylthebaol concentration would be between 3 ng/ml and 0.03 ng/ml assuming a similar excretion profile and Mexican or Middle Eastern Heroin being used. These low levels would be difficult to detect. If the 5-acetylthebaol is excreted slower than the morphine, it would be at a higher concentration relative to morphine in the time window that the morphine was at 300 ng/ml. This would make detection easier. In either case, the situation is much better than that of thebaine since the failure to detect 5-acetylthebaol would just let a guilty individual go free. Contrast that to the case for when thebaine is used as a marker, where missing low concentrations accuses an innocent party of Heroin use. Thebaine is only degraded to 5-acetylthebaol during conditions similar to that used in Heroin production. Just heating, as one would have during the cooking of poppy seeds degraded the thebaine but produces other types of products. Thus any 5-acetylthebaol or thebaol found in urine would indicate that sample came from a Heroin user.

**Other Impurities Present in Heroin but not Poppy Seeds**

Several compounds appear in Heroin but are absent in poppy seeds. A partial list of the more prevalent materials is given in Table 3.

**Table 3**

Phenobarbital and Methaqualone (present to extend Heroin high) - 10-20% of samples in 10% to equal concentrations to the Heroin

Quinine (present to give a bitter taste to cut material) - 50% of samples

Procaine (p-aminobenzoicacid ethyl ester; present as local anesthetic for injection) - 10-15% of samples

These materials are in varying concentrations and absent in appreciable numbers of Heroin samples. Quinine, present in the most heroin samples, also is present in tonic water. Thus quinine may be a poor marker for Heroin. Phenobarbital and methaqualone are

controlled substances and as such would not be available to the general public. Immunoassays are available for methaqualone and phenobarbital from Syva, and their presence could be readily determined. Syva's standard barbiturate assay has only a 10% cross-reactivity with phenobarbital (2000 ng/ml of phenobarbital would trip the 200 ng/ml barbiturate cut-off level used by the Navy). However, they market a more specific assay just for phenobarbital and diphenylhydantoin. The Rouch barbiturate Radioimmunoassay (RIA) also detects phenobarbital poorly (6% cross-reactivity, 3400 ng/ml of phenobarbital would trip the 200 ng/ml barbiturate cut-off level used by the Navy). Procaine is a non-controlled, local anesthetic. Since it may be in several consumer products and is in few Heroin samples it would also be a poor marker for Heroin use.

**Summary and Recommendations**

Three possibilities exist to distinguish between poppy seed ingestion and Heroin use. They are:

*First Recommendation*

The NDSL could consider using the ratio of thebaine to morphine in the urine of individuals who have morphine levels between 300 ng/ml and 4000 ng/ml. If this ratio fell within a range found in poppy seeds, that individual would be considered having a opiate positive due to poppy seed ingestion. If that range was lower or no thebaine was detected, that individual could be considered a Heroin user.

Before this recommendation could be implemented, the following research should be undertaken:

- The thebaine/morphine ratio of poppy seeds from a number of sources should be examined.
- The stability of thebaine in cooking should be addressed.
- A method of analysis of thebaine conjugates in urine should be developed.
- Several individuals should ingest a known amount of poppy seeds with known thebaine/morphine ratios and the ratio of thebaine/morphine determined as a function of time.

*Second Recommendation*

The NDSL could consider testing for 5-acetylthebaol or thebaol in the urine of individuals who have morphine levels between 300 ng/ml and 4000 ng/ml. If either was detected, then that individual would be considered positive for Heroin.

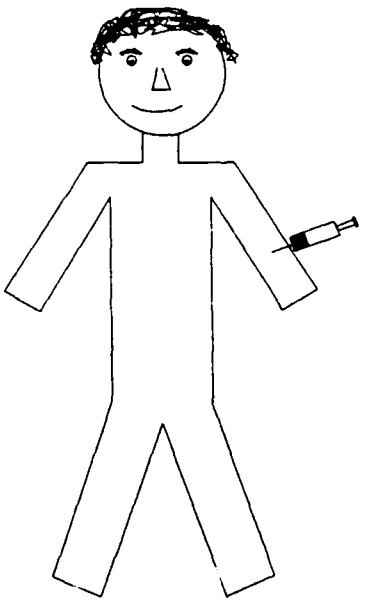
Before this recommendation could be implemented, the following research should be undertaken:

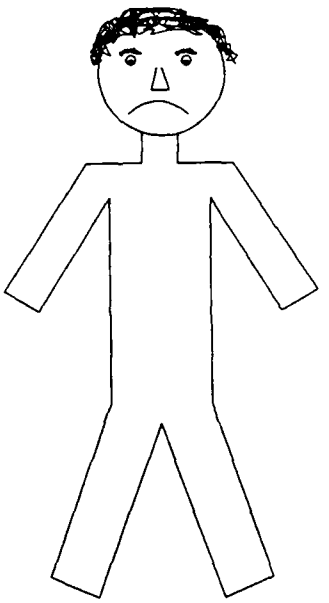
- A method of analysis of both 5-acetylthebaol and thebaol in urine should be developed.
- The presence of either compound in a moderate number of urine samples from suspected Heroin users should be established.
- The observation that thebaine does not produce these compounds when poppy seeds are cooked, under a variety of conditions, should be confirmed.

*Third Recommendation*

The NDSL should consider testing for phenobarbital and methaqualone by an immunoassay in the urine of individuals who have morphine levels between 300 ng/ml and 4000 ng/ml. If either is present in any level above the detection limit, that individual would be considered positive for Heroin. These tests could be easily implemented but confirmation methods for these compounds may be necessary before legal action could be taken.

**Summary of Compounds Present or Absent in Heroin and Poppy Seed Users**




| | HEROIN USER | POPPY SEED EATER |
|---|---|---|
| PRESENT: | Morphine<br>Codeine<br>6-Acetylmorphine?<br>Thebaol? | Morphine<br>Codeine<br>Thebaine? |
| ABSENT: | Thebaine? | 6-Acetylmorphine<br>Thebaol |